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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/068,507	07/15/98	EIJSINK V	1380-122PCT

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EXAMINER	
SLOBODYANSKY,E	
ART UNIT	**PAPER NUMBER**
1652	15

DATE MAILED: 05/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/068,507	Eijsink et al.
Examiner	**Group Art Unit**
Elizabeth Slobodyansky	1652

☒ Responsive to communication(s) filed on *Feb 29, 2000* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *16-43* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *16-43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed February 29, 2000 canceling claims 1-15 and adding claims 16-43 has been entered.

Claims 16-43 are pending.

A telephone call was made to Ms. Kristi Rupert on April 27, 2000 to inform her that in the previous Office action mailed September 29, 1999 words starting from "While" on page 5, line 6, and the entire line 7, have been typed in error and should not be considered as a part of the rejection.

Information Disclosure Statement

With regard to Applicants' remarks regarding the listing of references in the specification on pages 23-24, the examiner confirms that initialized references listed on form PTO-1449 have been considered. The examiner also cited some references on form PTO-892. If references cited on form PTO-892 were present in the listing, the examiner is still required to list them on form PTO-892 unless they were indicated on form PTO-1449. Those references cited in the listing that have not been indicated by Applicants on form PTO-1449 or by the examiner on form PTO-892 have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, 22 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 16, 17, 22 and 39 encompass a promoter inducible by the expression products of an IF, a SakK and a SakR genes of a lactic acid bacterium (LAB). The examiner is unable to locate adequate support in the specification for such claim. Applicants disclosed only one inducing agent, the expression product of the IF gene. There is no showing in the specification that said inducing agent can be substituted by the expression products of a SakK and a SakR genes of *Lactobacillus sake* LTH673 (LTH673) to induce the IF gene promoter. Furthermore, there is no indication that promoters of SakK and SakR genes of LAB inducible by the expression products of said genes were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claim 16, with dependent claims 17-36 and 41-43, and claim, 37-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 16, 37 and 39 encompass a genus of a promoter inducible by the expression product of an IF gene as well as a genus of an IF gene. Applicants disclose the promoter of the IF gene of LTH673 that is inducible by its expression product. This promoter has the nucleotide sequence set forth in SEQ ID NO:6. Applicants do not teach any other promoter that is inducible by the IF gene product (amino acid residues 19-37 of SEQ ID NO:3). There is also no teaching in the specification as to what are the common distinguishing features shared by the members of the genus of an IF promoter inducible by the expression product of an IF gene that would distinguish it from other promoters inducible by the expression products of their respective genes in bacteriocins' clusters. Thus, the representative number of species is one.

Therefore, based on the instant disclosure, taken into account that the representative number of the disclosed species equals one and considering the state of the relevant art, it is unpredictable whether a nucleotide sequence will be induced by the IF gene expression product. Thus, a promoter inducible by the expression product

of an IF gene lacks sufficient written description needed to practice the invention of claims 16, 37 and 39.

Claim 16, with dependent claims 17, 18, 20-36 and 41-43, and claim 37-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a promoter inducible by the IF gene expression product, does not reasonably provide enablement for a promoter inducible by a functional analogue of said gene product and a functional analogue of an IF gene product itself. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

In their Remarks filed February 29, 2000 Applicants argue that "the functional analogues are identifiable as being similar in sequence, and their function may be assayed by a simple Northern blot procedure" (page 11, last paragraph). It is agreed that the function can be assayed by Northern analysis in case of naturally occurring LAB promoters and IF gene products. However, the claims encompass engineered promoters and inducing agents of unknown structure. The following rejection is made over a promoter of an unknown structure inducible by a functional analogue of an IF gene expression product of an unknown structure.

The specification teaches one IF gene product that induces its promoter. A functional analogue of a gene product can be a compound of various chemical classes and not necessarily peptides. It is impossible to make a compound without knowing its structure. Consequently, it is impossible to make a promoter that is inducible by unknown compound. The specification lacks guidance as to what are other compounds in addition to amino acid residues 19-37 of SEQ ID NO:3 that can induce the IF gene promoter. Moreover, as mentioned above, an analogue can be any molecule. Therefore, the breadth of these claims is much larger than the scope enabled by the

specification. Therefore, one of ordinary skill would require guidance, such as information regarding the structural limitations on a promoter and a functional analogue of its gene expression product, in order to make a promoter inducible by a functional analogue of an IF gene, SakK gene and SakR gene as well as said analogues in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16, with dependent claims 17-36 and 41-43, and claims 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16, 38 and 39 recite an IF gene, a SakK gene and a SakR gene. While Applicants define these genes in LTH673, they did not define the genus of each gene. Claim 24 is drawn to plnA, plnB, plnC, and plnD genes as functional analogues of an IF gene, a SakK gene and a SakR gene. While claims 16, 38 and 39 are drawn to three genes, claim 24 is drawn to four. The correlation and difference between each gene recited in claim 16 and genes recited in claim 24 is not defined. Furthermore, both

claim 16 and 24 refer to genes in a lactic acid bacteria. It is confusing because it is unclear what is the difference between two sets of genes.

Claim 37 recites a K gene, a R gene, an IF gene, a T gene, an A gene of a lactic acid bacterium. These genes are defined for LTH673 on page 8, line 22, through page 9, line 20, of the specification. The difference between SakK and SakR genes of claim 16 and K and R genes of claim 37 is unclear. None of these genes is defined in a lactic acid bacterium. Applicants describe their invention as encompassing "a gene expression system, which comprises genes, promoter sequences and peptides involved in the production of bacteriocins except nisin in lactic acid bacteria" (page 5, lines 7-9). Such limitation, if included in a claim, would claim the invention by excluding what the inventors did not invent rather than distinctly and particularly pointing out what they did invent (MPEP 2173.05(i)). The claims recite functional analogues. There is no an art-accepted definition of said term.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16, with dependent claims 18, 24, 28 and 41-43, is rejected under 35 U.S.C. 102(b) as being anticipated by Diep et al. (1994).

Diep et al. (1994, form PTO-1449) teach that the genes of plnABCD cluster in *Lactobacillus plantarum* C11 are transcribed from a common promoter inducible by plantaricin (abstract). They cloned the entire unit that includes the regulatable promoter (page 161, 2nd column).

In their Remarks filed February 29, 2000 Applicants argue that "Diep et al. fails to disclose several important aspects of the present invention" (page 15, 2nd paragraph). They further indicate that "Diep et al. did not know or publish the function of plnA" (page 15, 3rd paragraph). However, these arguments are not persuasive in relation to the invention as claimed. Diep et al. teach a vector comprising a promoter that is inducible by its gene expression product (page 161, 2nd column). The inducibility is an inherent characteristic of said promoter. Therefore, the Diep et al. reference anticipates claim 16.

Claim 16, with dependent claims 17-19, 21, 22, 28 and 41-43, is rejected under 35 U.S.C. 102(b) as being anticipated by Tichaczek et al.

Tichaczek et al. (1994, form PTO-1449) teach the expression of sakacin P in LTH673. They teach a vector comprising a promoter inducible by its gene expression product (abstract; page 362, "Methods"; page 363, Figure 2). The inducibility is an

inherent characteristic of said promoter. Therefore, the Tichaczek et al. reference anticipates claims 16, 38 and 39.

Claim 16, with dependent claims 18, 20-36 and 41-43, and claims 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Diep et al. (1995).

Diep et al. (1995, form PTO-1449) teach that plantaricin A induces its own production by stimulating transcription of the *plnABCD* operon in *Lactobacillus plantarum* C11 (abstract; page 632, left-hand column, 1st paragraph; page 634, right-hand column; page 636, right-hand column, 1st paragraph). They teach that two-component regulatory systems located in nisin, subtilin, epidermin and sakacin A gene clusters are essential for the production of these bacteriocins (page 632, left-hand column, 2nd paragraph). They teach that production of bacteriocins is a regulated process. They teach that bacteriocin production in *Lactobacillus plantarum* C11 is an inducible process. They teach the heterologous expression of *plnABCD* that can be induced by plantaricin A (page 637, paragraph bridging two columns; page 638, left-hand column, last paragraph).

In their Remarks filed February 29, 2000 Applicants argue that "[t]he publication date of the Diep et al. reference is December 13, 1995. ... Therefore, Diep et al. is not prior art" (page 17, 1st paragraph). The cover page of the issue indicates only November 1995. Absent evidence to the contrary, the day is presumed to be the 1st.

There is no evidence of record showing that the publication of this particular issue has been postponed until after its printed issue date. Therefore, the Diep et al. reference (1995) anticipates claims 16, 18, 20-36 and 38-43.

Claim 16, with dependent claims 17-19, 21, 22, 28 and 41-43, is rejected under 35 U.S.C. 102(b) as being anticipated by Axelsson et al.

Axelsson et al. (form PTO-1449) teach the expression of sakacin A in *Lactobacillus sake* Lb706. They teach a vector comprising a promoter inducible by its gene expression product (abstract; pages 2126-2127). The inducibility is an inherent characteristic of said promoter. Therefore, the Axelsson et al. reference anticipates claim 16.

Claim 16, with dependent claims 18, 24, 28 and 41-43, is rejected under 35 U.S.C. 102(b) as being anticipated by Venema et al. (1994).

Venema et al. (1994, form PTO-1449) teach that the genes of pedABCD cluster of *Pediococcus acidilactici* that produces pediocin are transcribed from a common promoter (abstract). They cloned the entire unit that includes the regulatable promoter (page 516, Figure 1).

Claim 16, with dependent claims 18, 24, 28 and 41-43, is rejected under 35 U.S.C. 102(b) as being anticipated by Balaban et al.

Balaban et al. (form PTO-1449) teach that the production of exoproteins in *Staphylococcus aureus* is controlled by a global regulatory system, *agr* (abstract). They show that this system is autoinducible (abstract). Claims 16, 38 and 39 are drawn to a functional analogues of genes of a lactic acid bacterium. *Staphylococcus* is the lactic acid bacterium. Therefore, the Balaban et al. reference anticipates claim 16.

Response to Arguments

Applicant's arguments filed February 29, 2000 have been fully considered but they are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., for example, that an inducing agent and a bacteriocin are different peptides) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically

pointing out how the language of the claims patentably distinguishes them from the references.

Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which they think the claims present in view of the state of the art disclosed by the references cited or the rejections made.

Applicants argue that an example of a functional analogue of the inducing agent of the instant invention is plantaricin A (page 15, last paragraph). They further explain that the common feature of the inducing agent of the instant invention and plantaricin A is the lack of a bacteriocin activity. They assert that the lack of a bacteriocin activity makes the inducing agent of the instant invention different from nisin.

It is known in the art that the production of many bacteriocins is inducible by the expression products of the genes of a bacteriocin gene cluster. It is also known that these clusters include two-component regulatory system. While plantaricin A has a common feature with the instant inducing agent, it has a common feature with nisin as well. Like in the nisin system, in the plantaricin system the inducing peptide and the bacteriocin are products of the same gene. Therefore, it appears that in most cases the production of bacteriocin in LAB is induced by the expression product of a gene of a bacteriocin gene cluster. Applicants fail to point out the features of a bacteriocin cluster

that impart the ability to produce both an inducing agent and a bacteriocin wherein they are not the same.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD

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